nucleoid by bending, wrapping or bridging DNA. The Histone-like Nucleoid Structuring protein H-NS can bridge DNA by binding to two separate DNA duplexes, or shield the DNA by binding to distant sites on the same duplex, depending on external conditions. H-NS occurs in Gram-negative enterobacteria and silences genes involved in bacterial virulence and antibiotic resistance. The current view reflects that the formation of an H-NS - DNA assembly starts with the initial binding of an H-NS dimer to a specific nucleotide sequence, followed by additional H-NS dimers interacting with bound H-NS and binding to adjacent sites on DNA. Several nucleotide sequences have been identified to which H-NS binds strongly. Despite enormous progress in methods aimed at resolving molecular structures, which resulted in resolving the structures of the dimerization domain and the DNA binding domain, it is still impossible to experimentally obtain detailed structural information of the entire complex, whereas dynamic properties are even harder to investigate in experiments. Molecular simulation can complement experiments by modeling the dynamical time evolution of biomolecular systems in atomistic detail. Employing molecular dynamics simulations, we studied the binding mechanism of H-NS to DNA. Our results show that H-NS binds strongly to AT-rich dsDNA in the minor groove. Furthermore, we found that H-NS binds transiently to dsDNA with high GC content, in the major groove. These observations are in excellent agreement with experimental data. By using transition path sampling, we were able to further probe the mechanism of H-NS binding to AT-rich DNA, resulting in the identification of two different modes of interaction.

**2723-Pos Board B153**

**The Binding Landscapes of the H3/H4 and CENP-A/H4 Dimers**

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Centromere protein A (CENP-A) is a centromere-specific variant of histone H3 and shares almost 50% amino acid identity to canonical histone H3. CENP-A is required for packaging the centromere, to facilitate separation of sister chromatids during mitosis. Indeed, significant structural similarities have been reported to exist between CENP-A/H4 dimers and H3/H4 dimers in co-crystals. In this work, we used molecular dynamics simulations to map the binding free energy landscape for the CENP-A/H4 and H3/H4 dimers. The Associated memory, Water mediated, Structure and Energy Model (AWSEM) and umbrella sampling constraints were applied for each simulation system towards obtaining two-dimensional free energy profiles of monomeric protein association and folding. Surprisingly, our calculations revealed significant thermodynamic distinctions between dimerization profiles of CENP-A/H4 and of H3/H4 pairs. Furthermore, we also investigated the actions of various histones chaperones, finding that free energy landscapes of the CENP-A/H4 dimer is significantly remodeled in the presence of its cognate chaperone HJURP. The obtained results are in general agreement with the available experimental data and provide new thermodynamic insights into the mechanisms that form the basis of canonical and histone variant CENP-A nucleosomes assembly in vivo.

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**Topological Polymorphism of Two-Start Nucleosome Fibers: A Stereochemical Analysis**

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The spatial organization of nucleosomes in 30-nm fibers remains unknown in detail. To address this issue, we analyzed all stereochemically possible configurations of two-start nucleosome fibers with short DNA linkers L = 13 - 37 bp (nucleosome repeat length NRL = 160 - 184 bp). Four superhelical parameters – inclination of nucleosomes, twist, rise and diameter – uniquely describe a uniform symmetric fiber. The energy of a fiber is defined as the sum of four terms: elastic energy of the linker DNA, steric repulsion, electrostatics and a phenomenological (H4 tail - acidic patch) interaction between two stacked nucleosomes. By optimizing the fiber energy with respect to the superhelical parameters, we found two types of topological transition in fibers (associated with the change in inclination angle): one caused by an abrupt 360° change in the linker DNA twisting, and another caused by over-crossing of the linkers. (The first transition is characterized by change in the DNA linking number, $\Delta Lk = 1$, and the second one by $\Delta Lk = 2$.) To the best of our knowledge, this topological polymorphism of the two-start fibers was not reported in the computations published earlier. Importantly, the optimal configurations of the fibers with linkers L = 10n and 10n+5 bp are topologically different. Our results are consistent with experimental observations, such as the inclination 60-70° (the angle between the nucleosomal disks and the fiber axis), helical rise, diameter and left-handedness of the fibers. In addition, we make several testable predictions, among them existence of different degree of DNA supercoiling in the fibers with L = 10n and 10n+5 bp, different stiffness of the two types of fibers, and a correlation between the local NRL and the level of transcription in different parts of the yeast genome.

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**Multivalent Targeting of Nucleosomes by the BRG1 At-Hook and Bromodmain**

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Beyond providing an avenue for packaging the genome into the nucleus, chromatin provides elegant mechanisms for the dynamic regulation of the eukaryotic genome. Chromatin structure undergoes dramatic spatial and temporal reorganizations throughout the life cycle of the cell, which require extensive remodeling of the nucleosome, the basic subunit of chromatin. A major mechanism for modulating chromatin structure is through ATP driven nucleosome remodeling. The switching/sucrose non-fermenting (SWI/SNF) chromatin remodeling complex facilitates ATP dependent remodeling of nucleosomes critical in gene regulation. SWI/SNF activity is mediated by one of two possible ATPases, Brahma (BRM) or Brahma related gene 1 (BRG1). The chromatin targeting, occupancy and activity of the complex are positively affected by histone acetylation, and it has been found that this is mediated through the C-terminal Bromodomains (BDs) of BRG1 and BRM. One possible mechanism for this is that BD recognition of acetylated histones targets and/or retains SWI/SNF at chromatin leading to increased activity. This is supported by previous reports of acetylation and BD dependent recruitment and retention of SWI/SNF at gene promoters. However, the BRG1 BD has been shown to have very poor affinity and conflicting specificity for acetylated histone peptides in vitro, calling into question the importance of this interaction. We propose that the nucleosome context is critical for proper activity of the BD in binding acetylated histones, and suggest that an adjacent AT-hook DNA binding domain contributes to BD activity. Here we present our recent results using NMR spectroscopy and TIRFM to investigate the multivalent interaction of the BRG1 AT-hook and BD with nucleosomes, including details of the structural basis by which the AT-hook-BD motif interacts with the 601-mononucleosome, the kinetic and thermodynamic basis of complex formation, as well as the effect of histone acetylation.

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**Quantification of Interphase Chromatin Dynamics in Fission Yeast**

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In mammals and other higher organisms, interphase chromosomes remain separated from each other and compartmentalized into chromosome territories. In yeast, chromosomes adopt a Rabl configuration, with arms extending from centromeres tethered at the spindle pole body(SPB), functionally equivalent to the centrosome, to telomeres at the opposite nuclear envelope. These organizations generally constrain chromatin motion, and contribute to gene positioning inside the nucleus. On the other hand, active genes escape from such physical constraints and are located at active regions such as transcription factories and nuclear pore complexes(NPCs). In spite of extensive studies for these phenomena, how gene loci sustain and change their positioning during the cell cycle still remains unclear. In order to elucidate chromatin dynamics during interphase, we visualized several gene loci and the centromeres (and the SPB) on the fission yeast *S. pombe* chromosomes that show a Rabl configuration, and then tracked the positions of the loci on a longer time scale than conventional one. The statistical analysis of the physical distance from the SPB to each locus suggested that the gene loci show not only restricted diffusion due to the physical constraint of the Rabl configuration, but also a novel dynamic property, that is quite different from simple diffusive behaviors reported so far. In this presentation, we will discuss functional roles that such chromatin dynamics possibly play within the interphase nucleus.

**2727-Pos Board B157**

**Effect of Architecture of Cell Nucleus on the Folding Principles of 3D Genome of Budding Yeast**

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Architecture of the cell nucleus and the spatial organization of genome are critical for nuclear functions. Single-cell imaging techniques and chromosome conformation capture (3C) based methods provide a wealth of information on the spatial organization of chromosomes. Computational tools for modeling